Role of CA-125 in Identification of Right Ventricular Failure in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating disease. Cor pulmonale, characterized by right ventricular (RV) failure, can severely influence prognosis in these patients. Hence, early recognition might be important for tailoring therapy. An old biomarker, CA-125, seems to be associated with the right heart. We aimed to show the relationship between CA-125 levels and RV failure in patients with COPD.

Hypothesis: CA-125 might be a useful biomarker in identification of RV failure in patients with COPD.

Methods: Forty patients with recent exacerbation of COPD were enrolled into the study. Another 40 age- and sex-matched individuals were enrolled for comparison. Levels of CA-125 were measured in the patients during the hospital stay. The COPD patients underwent echocardiographic study on the same day. Right-ventricular parameters were evaluated, and RV failure was identified via transthoracic echocardiography.

Results: Patients with COPD had significantly higher CA-125 levels compared with controls (median 33.94 U/mL vs 9.76 U/mL, respectively; $P < 0.001$). Levels of CA-125 were correlated with systolic pulmonary artery pressure ($r = 0.550$, $P < 0.001$), tricuspid annular plane systolic excursion ($r = -0.496$, $P = 0.001$), and tricuspid lateral annulus S velocity ($r = -0.549$, $P = 0.002$). High CA-125 levels, obtained in hospitalized patients with COPD before echocardiography, enabled identification of RV failure with a sensitivity of 89.5% and specificity of 85.7%.

Conclusions: The CA-125 biomarker can be used to identify COPD patients with RV failure.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating disease that limits the survival and quality of life of patients.^{1–3} These patients experience frequent episodes of exacerbation during the course of their illness, and eventually right ventricular (RV) failure, cor pulmonale, begins to accompany the clinical picture, with a further worsening of the prognosis.^{4,5} Transthoracic echocardiography is a well-established imaging modality in the diagnosis of not only left-sided pathologies, but also right-sided pathologies of the heart.⁶ However, due to a poor acoustic window, COPD patients are not good candidates for echocardiographic examination, and, right-heart evaluation requires further expertise. Tumor markers, which help with diagnosis and prognostication of cancer diseases, were shown previously to be elevated in non-neoplastic diseases.⁷ Furthermore, CA-125, CA-19.9, and carcinoembryonic antigen were previously shown to be related to severity of COPD.⁸ Recently, CA-125, known to

be produced by epithelial ovarian tumors, has been shown to be associated with RV dilation in a retrospective study.⁹ Previous studies indicated that the half-life of CA-125 varied from 5–7 days to several days in different studies.^{10,11} It is hypothesized that normal, or so-called stressed, mesothelial cells produce CA-125 in response to hemodynamic and/or inflammatory stimuli.¹² The biomarker CA-125 seems to be different from other biomarkers such as natriuretic peptides, which are released secondary to acute stress. Hence, CA-125 might help identification of RV dysfunction, which imposes stress on the splanchnic bed, in patients with COPD before it becomes clinically apparent cor pulmonale. We aimed to show whether measures of RV function could be related to CA-125 levels among patients with COPD.

Methods

Forty consecutive patients with moderate to severe COPD, who had at least a 10-year history of COPD and who were hospitalized with exacerbation, were enrolled into the current study after obtaining informed consent. An additional 40 age- and sex-matched healthy individuals with prior CA-125 levels were enrolled as a control group. None of the COPD patients or control group had

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history or current evidence of malignancy. The study was performed in accordance with the Declaration of Helsinki for Human Research, and was approved by the institutional review board. All COPD patients, who had ≥ 1 COPD exacerbation previously, underwent detailed physical examination and respiratory testing by an expert chest physician.

Disease severity of the COPD patients was evaluated based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease according to respiratory-function tests.⁴ Respiratory-function testing was also performed with a spirometer (Vmax Series 20C, SensorMedics, Yorba Linda, CA) at least 3 times in sitting posture after being trained for forced vital capacity maneuver during stable period. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) were measured, and best results were recorded as absolute (mL) and percentage (percentage of expected) values.¹

All patients underwent routine laboratory investigation at admission, and serum CA-125 levels were obtained after initial stabilization during hospital stay. Serum levels of CA-125 were determined using a commercially available kit (AxSYM System, Abbott Laboratories, Abbott Park, IL). The AxSYM CA-125 assay is based on microparticle enzyme immunoassay; this technology uses a solution of suspended, submicron-sized latex particles to measure analytes. Patients were classified into 2 groups based on CA-125 level, normal CA-125 (<35 U/mL) and high CA-125 (≥ 35 U/mL), according to our laboratory reference limits and a previous study.^{9,13}

In the same day, all patients underwent transthoracic echocardiography by an experienced echocardiographer blinded to the study plan; echocardiographic examinations were performed via the Vivid 7 system (GE Healthcare, Wauwatosa, WI) with 2.5–5-MHz probes. Digital records of echocardiographic examinations were evaluated offline. Ejection fraction (EF) was calculated by modified Simpson method. Chamber sizes were defined according to recent guidelines.¹⁴ Right ventricular dimensions were evaluated according to the most recent guideline¹⁴: RV dimension >3.4 cm at basal plane or >3.8 cm at midplane was used to designate moderate RV dilation as per guidelines. Those with moderate to severe dilation of RV according to guideline thresholds were considered to have significant RV dilation. Right atrium (RA) size was measured on minor-axis dimension extending from the lateral border of the RA to the interatrial septum.¹⁴ The left atrium size was measured at end-ventricular systole by M-mode linear dimension, obtained from the parasternal long-axis view. Systolic pulmonary artery pressure (SPAP) was calculated as shown previously.¹⁵ Presence or absence of pericardial effusion was noted. Tricuspid annulus velocities, RV outflow tract acceleration time (RVOTaccT), and tricuspid annular plane systolic excursion (TAPSE) were measured accordingly.^{16–18} Valvular regurgitations were graded into 4 categories (trivial, mild, moderate, and severe) via combination of color flow jet Doppler signal intensity, vena contracta width according to guideline recommendations.¹⁹ Right ventricular failure was defined by the combination of TAPSE and lateral wall tissue Doppler systolic (S) velocity

according to previous thresholds (S velocity <10 cm/sec and TAPSE <18 mm were used to define significant RV dysfunction),^{18,20–22} in addition to the presence of signs and symptoms of right-heart failure (according to clinical notes at admission)—mostly pretibial edema, with some patients exhibiting jugular-vein distention and a few who had ascites during admission.

Intraobserver variability of echocardiographic measurements was evaluated by analyzing parameters in 10 randomly selected subjects. Intraobserver variability, calculated via Bland-Altman analysis, ranged from 6% to 11% for all measurements. Hypertension was defined as blood pressure $>140/90$ mm Hg on >2 occasions during office measurements or being on antihypertensive treatment. Diabetes mellitus was defined as fasting blood sugar ≥ 126 mg/dL or being on antidiabetic treatment. Those who continued smoking were considered as current smokers. Patients with previous history or suspicion of malignancy, patients with active inflammatory disease including those during index exacerbation yielding hospitalization of the patient (pulmonary infection, $n = 10$), patients with signs of inflammation (C-reactive protein >10 mg/L), and patients with significant accompanying left-heart pathology ($n = 8$) were excluded from the analysis.

Statistical Analysis

Parametric data were expressed as mean $\pm$ SD or median (range) and categorical data as percentages. Statistical procedures were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). Independent parameters were compared via independent samples *t* test. The Mann-Whitney *U* test was used to test parametric data without binomial distribution. Categorical data were evaluated by χ^2 test as appropriate. Correlation was evaluated by Pearson correlation test or Spearman correlation test. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of CA-125 (at which sensitivity and specificity would be maximal) for the prediction of RV failure and RV dilation. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with use of the *Z* test. Multivariable logistic regression was used to evaluate independent parameters affecting high CA-125 levels (≥ 35 U/mL). A *P* value ≤ 0.05 was considered significant.

Results

The mean age of the patients was 64 ± 8.7 years (range, 49–82 years; 24 females, 16 males) and was not different from the control group at 61 ± 13.4 years (range, 26–79 years; 22 females, 18 males), *P* = 0.231 and *P* = 0.821, respectively. Levels of CA-125 were significantly higher in patients with COPD compared with controls (median 33.94 U/mL; range, 5.51–351 vs median 9.76 U/mL; range, 0–60.97, *P* < 0.001). The median COPD stage was stage 3 (16 patients in stage 2, 14 patients in stage 3, and 10 patients in stage 4). Individually, the median CA-125 level of the control group was not significantly different from COPD stage 2 patients (median 11.38 U/mL, *P* = 0.261), whereas CA-125 levels of patients with stage 3 and 4

Figure 1. Graphic representation of median levels of CA-125 in the control group and patients with 3 different stages of COPD in the study. Vertical axis denotes CA-125 levels in U/mL. Abbreviations: COPD, chronic obstructive pulmonary disease.

COPD individually were significantly higher than controls and stage 2 COPD patients ($P < 0.001$ for all, Figure 1). Furthermore, median CA-125 level in stage 4 COPD patients was higher than in stage 3 COPD patients ($P = 0.001$). Of note, all COPD patients had been well treated with diuretics and other therapies, and during echocardiography no patient had significant pretibial edema or ascites. Mean EF was $58.5\% \pm 6.6\%$, and mean SPAP was 35.7 ± 14.4 mm Hg in COPD patients. None of the COPD patients had accompanying left ventricular diastolic dysfunction. In the COPD patients, CA-125 levels were significantly and moderately correlated with FEV1/FVC ($r = -0.466$, $P = 0.002$), COPD severity ($r = 0.549$, $P < 0.001$), SPAP ($r = 0.550$, $P < 0.001$), TAPSE ($r = -0.496$, $P = 0.001$), and tricuspid lateral annulus S velocity ($r = -0.549$, $P = 0.002$). Of note, there was no significant correlation between CA-125 level and EF, RVOTaccT, creatinine level, hemoglobin level, and age in the study subjects ($P > 0.05$). Level of CA-125 was also correlated with severity of tricuspid regurgitation ($r = 0.390$, $P = 0.013$) and with RA size ($r = 0.472$, $P = 0.048$). High CA-125 levels were associated with atrial fibrillation, presence of RV dilation, presence of RV failure, and tricuspid regurgitation, whereas they were not associated with gender, presence of hypertension, diabetes mellitus, smoking status, and presence of pericardial effusion in the patient cohort (Table 1).

Factors associated with high CA-125 levels were enrolled into multivariable logistic regression (COPD severity, FEV1/FVC, rhythm, tricuspid regurgitation, SPAP, and RV failure), and it was found that presence of RV failure was the only parameter independently associated with high CA-125 levels in patients with COPD ($P = 0.021$, ExpB = 33.207).

Levels of CA-125, obtained prior to echocardiography, were predictive of presence of RV failure, with AUC of 0.902 (Figure 2; 95% confidence interval [CI]: 0.801–1.00, $P < 0.001$), and RV dilation with AUC of 0.775 (Figure 3; 95% CI: 0.630–0.920, $P = 0.003$). High CA-125 levels (≥ 35 U/mL) in hospitalized patients with COPD identified RV failure with a sensitivity of 89.5% and specificity of 85.7%, with positive predictive value of 85% and with negative predictive value of 90%. High CA-125 levels increased the risk of having

Table 1. Demographic and Selected Clinical Data of Study Subjects According to Normal and High CA-125 Levels

	High CA-125 (≥ 35 U/mL)	Normal CA-125 (< 35 U/mL)	P Value
Age, y	65.7 $\pm$ 9.8	62.3 $\pm$ 7.1	0.212
Gender, M/F	7/13	9/11	0.374
COPD stage [1/2/3/4], (n)	0/2/10/8	0/14/4/2	0.001
HT	15/20	11/20	0.160
DM	3/20	1/20	0.302
Current smoking	6/20	9/20	0.257
Permanent AF ^a	9/20	2/20	0.015
EF (%)	57.8 $\pm$ 7.6	59.3 $\pm$ 5.4	0.463
Systolic pulmonary artery pressure (mm Hg)	43.3 $\pm$ 12.3	28.1 $\pm$ 12.2	<.001
Presence of RV dilation (n)	16/20	7/20	0.005
Presence of RV failure	17/20	2/20	<.001
RVOTaccT (msec)	96.9 $\pm$ 31.5	113.8 $\pm$ 31.3	0.101
TAPSE (cm)	1.7 $\pm$ 0.3	2.2 $\pm$ 0.2	<.001
Tricuspid lateral annulus S velocity (cm/sec)	6.4 $\pm$ 1.8	8.9 $\pm$ 1.8	<.001
Right atrium minor axis (cm)	5.4 $\pm$ 0.8	4.7 $\pm$ 0.5	0.05
Pericardial effusion (n)	2/20	2/20	0.698
Mitral regurgitation (trivial/mild/ moderate/severe)	6/11/3/0	8/11/1/0	0.359
Tricuspid regurgitation (trivial/mild/ moderate/ severe)	1/13/5/1	7/10/3/0	0.013
Aortic regurgitation (trivial/mild/ moderate/severe)	16/4/0/0	16/2/2/0	0.454
Cr (mg/dL)	1.0 $\pm$ 0.5	1.0 $\pm$ 0.1	0.476
Hemoglobin (gr/dL)	14.4 $\pm$ 1.9	14.4 $\pm$ 2.0	0.994
FEV1	39.9 $\pm$ 14.2	56.5 $\pm$ 16.5	0.002
FEV1/FVC	58.4 $\pm$ 10.3	65.0 $\pm$ 6.8	0.021

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; Cr, creatinine; DM, diabetes mellitus; EF, ejection fraction; F, female; FEV1/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity; HT, hypertension; M, male; RV, right ventricular; RVOTaccT, right ventricular outflow tract acceleration time; TAPSE, tricuspid annular plane systolic excursion.

^aAfter follow-up.

Figure 2. An ROC curve to identify RV failure with CA-125 in patients with COPD (AUC: 0.902, $P < 0.001$). Abbreviations: AUC, area under the curve; COPD, chronic obstructive pulmonary disease; ROC, receiver operating characteristic; RV, right ventricular.

Figure 3. An ROC curve to identify RV dilation with CA-125 in patients with COPD (AUC: 0.775, $P = 0.003$). Abbreviations: AUC, area under the curve; COPD, chronic obstructive pulmonary disease; ROC, receiver operating characteristic; RV, right ventricular.

the diagnosis of RV failure by echocardiography by 51-fold (odds ratio, 95% CI: 7.567–343.731).

Discussion

Chronic obstructive pulmonary disease is a debilitating disease with frequent exacerbations. The prognosis is further compromised with the addition of RV failure. Hence, it may be important to recognize the situation early in order to intervene timely with the aim to improve patient quality of life. Biomarkers are needed to designate the severity of COPD.⁸ Herein, CA-125 levels, which were shown to be independently influenced by right heart chambers, could be helpful.^{9,23} In this study, CA-125 levels, obtained after initial stabilization, were related with COPD severity as well. Moreover, CA-125 levels were indicative

of RV failure, a major cause of morbidity and mortality in these patients.²⁴ Early recognition of RV failure, before it becomes clinically apparent cor pulmonale, might bring about improved survival.²⁵

For recognition of RV failure, clinical examination, chest x-ray, and electrocardiography might be utilized. However, all these parameters lack sensitivity and specificity for RV failure, although electrocardiography may have a prognostic role.²⁶ Echocardiography remains as a primary noninvasive tool for accurate diagnosis of RV failure. However, echocardiographic windows for accurate evaluation of RV are not easy to obtain in COPD patients, and evaluation of RV requires further expertise. Of note, all patients in this cohort had varying degrees of echocardiographic evidence of RV hypertrophy. However, almost one-half had echocardiographic evidence of RV failure, and this was compatible with the previous literature.²⁷ So far, brain natriuretic peptide was previously shown to be related to clinically apparent RV failure in patients with COPD.²⁸ In that study, patients with clinically diagnosed cor pulmonale had higher brain natriuretic peptide levels than both non-cor pulmonale patients and controls. However, we think it might be more important to recognize these patients earlier to tailor therapy, and a more precise definition of RV failure seems necessary in patients with COPD, because accompanying left-sided heart diseases remain as a potential confounder. In our study, CA-125 levels were significantly higher in patients with RV failure, and CA-125 levels were finely correlated with markers of RV dysfunction and pulmonary artery pressure, which was not independently related to CA-125 levels. Although elevated pulmonary artery pressure causes RV failure in patients with COPD, it seems that RV failure, rather than pulmonary artery pressure, is responsible for elevation of CA-125 levels following congestion of splanchnic mesothelium, which is thought to be the primary source of CA-125. Therefore, CA-125 might provide an opportunity window for early recognition and tailored therapy of RV failure, because now it is relatively established that progression rate of pulmonary artery pressures and relative resistance of RV to failure are not predictable in every patient.^{29,30}

There are some limitations of the study worth mentioning. First, our study was not designed to establish a cause-and-effect relationship; hence, we need prospective follow-up studies. The sample size is relatively small and CIs are large; the results should be interpreted with that in mind. However, considering even the lowest end of CI seems to add significant predictive value. The enrolled patients were living in a city (Sivas) situated at a high altitude, which may possibly alter the results (higher pressures, severe deterioration). Patients were evaluated after a recent worsening of COPD, which may influence both pressures and RV function. It is important to note that all evaluations, both CA-125 levels and echocardiography, were performed when the patients were stabilized. The preference of blood samples obtained after initial stabilization instead of admission samples might be criticized; however, it should be kept in mind that the half-life of CA-125 is considerably long, and so far, there is no study for kinetics in heart failure. Hence, samples obtained after initial stabilization do not mean to indicate prognosis. Besides, during acute episodes

there are many confounders, mainly inflammatory stimuli, that may have yielded conflicting results, as pointed out previously.¹² Furthermore, compared with gynecological oncology, cardiovascular medicine is not as well educated in CA-125. Criticisms raised to compare the kinetics of CA-125 to other well-known biomarkers, such as natriuretic peptides, are largely speculative, because this biomarker is different. Results should be confined to more severe patients who experienced a recent exacerbation.

Conclusion

In this study, echocardiographically defined RV failure was chosen as the target because clinically apparent cor pulmonale might be too late to intervene. Of note, none of the patients had clinically ascertainable congestion, necessary for clinical diagnosis of cor pulmonale. Therefore, influence of CA-125 levels in clinically apparent cor pulmonale or clinically stable COPD patients may be different. Nonetheless, close association of CA-125 levels with parameters of RV dysfunction and pathophysiological rationale render CA-125 an attractive tool for accurately identifying patients with RV failure before referral to echocardiography and before they develop overt cor pulmonale. We believe further studies are needed in which CA-125 is used to risk-stratify patients with COPD based upon its performance on identification of RV failure in patients with COPD.

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